

Fracture Table vs. Lateral Positioning for Intramedullary Fixation of Femur Fractures (The FLiP Study): A protocol for a pilot randomized controlled trial

Background: Femoral Shaft fractures are devastating and life threatening injuries. Femoral shaft fractures are most commonly treated with intramedullary fixation. Malrotation of the injured limb after fixation is a common and significant complication following femoral shaft fractures. During the operation, patients can be positioned either supine or in a lateral position. Additionally, patients can be placed on a standard radiolucent operating room table, or placed on a fracture table with traction statically applied to the operative limb throughout the case. Previous case series and cohort studies have shown equivalence between study groups, but choice between positioning options remains controversial.

Methods: This represents a protocol for a randomized controlled pilot trial. We will be compared lateral positioning with use of manual traction to supine positioning with use of a fracture table. Primary outcomes will be in assessment for feasibility for a future full scale randomized trial, including evaluating patient recruitment, patient compliance with followup, contamination between treatment arms and others.

Results: The primary outcome will be feasibility for a future trial. Secondary outcomes will include malrotation as measured through postoperative computed tomography scans and gait analysis at 6 months.

Fracture Table vs. Lateral Positioning for Intramedullary Fixation of Femur Fractures (The FLiP Study): A pilot cluster randomized crossover trial

Study Protocol

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
FLiP	Fracture table vs. Lateral Position
AFFF	Antegrade Fixation of Femur Fracture
CEO	Centre for Evidence Based Orthopedics
EQ-5D	Five level health-related quality of life measurement, developed by Euroqol Group
IMN	Intramedullary Nail

TRIAL SUMMARY

Full Title	Fracture Table vs. Lateral Positioning for Intramedullary Fixation of Femur Fractures (The FLiP Study)
Short Title	FL(i)P Pilot Trial
Methodology	Pilot cluster randomized crossover trial design
Methods Centre	The Centre for Evidence-Based Orthopaedics, McMaster University
Study Sites	4 clinical sites will participate in the pilot study.
Pilot Study Objectives	The primary objective of this pilot trial is to assess the feasibility of a definitive cluster randomized crossover trial to determine the effect of lateral patient positioning versus supine positioning with fracture table use for reamed antegrade intramedullary fixation of femur fractures.
Definitive Trial Objectives	<p>The primary objective of the definitive trial is to determine if lateral positioning yields better rotational alignment of the operative limb. This will be determined through post-operative computer tomography (CT) scans.</p> <p>The secondary objectives of the definitive trial are to determine if lateral positioning significantly affects health-related quality of life, operative time, use of intraoperative fluoroscopy, conversion to open surgery, and complications from use of the fracture table or from lateral positioning.</p>
Sub-Study Objectives	A sub-study will be conducted to determine if lateral positioning affects functional gait abnormalities.
Population	Patients aged 18 and older presenting to participating clinical sites with diaphyseal femur fractures.
Treatment Groups	<p>This is a cluster randomized crossover trial assessing two options for intraoperative patient positioning:</p> <ul style="list-style-type: none"> • Lateral position with manual traction • Supine position with fracture (traction) table
Feasibility Outcomes	<ol style="list-style-type: none"> 1. Ensure 90% of eligible patients are enrolled 2. Achieve 90% compliance with the randomization treatment allocations 3. CT scans obtained within 6 weeks of their fracture in 95% of participants 4. 95% completed data collection on randomization, baseline, and surgical case report forms, and 90% complete follow-up data on the case report forms
Definitive Trial Outcomes	<ul style="list-style-type: none"> • Malrotation of operative limb, measured through postoperative CT scan to calculate degree of rotation compared to contralateral side (Primary outcome for the definitive trial) • Health-related quality of life as measured by the EuroQol-5 Dimensions (EQ-5D) • Operative time • Fluoroscopy time • Conversion to open surgery • Operative table complications

	<ul style="list-style-type: none"> Functional gait abnormalities as measured through gait analysis (Sub-study)
Sample Size	Approximately 100 participants across 2 clinical sites.
Timeline	Clinical sites will enroll for 4 months (to allow for 1 crossover). Participants will be followed for 6-months post-fracture.

1.0 BACKGROUND AND RATIONALE

Femoral shaft fractures are common and severe injuries that typically occur alongside other complex, high-energy injuries in the poly-traumatized patient. Femur fractures can yield extensive bleeding and muscle injury of the thigh, and have a high worldwide burden; occurring at a rate between 14 and 42.5 /100,000 person years, with approximately 1 in 10 road traffic accidents worldwide involving a femoral shaft fracture treated by surgery¹. Additionally, there is a significant disparity of burden for diaphyseal femur fractures, with 91% occurring in lower middle class income countries, with the majority affecting younger males.²

To help mitigate the effects of ongoing blood-loss, worsening inflammation and pain from the unstable fracture ends, femoral shaft fractures require urgent management using either an early total-care or damage-control orthopaedics approach^{3,4,5}. Associated injuries, markers of resuscitation, and overall patient stability guide operative decision making on timing of surgical intervention⁶. Definitive internal fixation using reamed, locked intramedullary nailing has become the standard of care in the adequately resuscitated patient⁷ as it provides fracture stability while facilitating nursing care and patient mobilization^{8,9}. Multiple femoral intramedullary nail techniques exist, however most femoral shaft fractures can be treated with an antegrade nail using either supine (fracture table) or lateral (free-leg drape) positioning^{10,11}. Fracture pattern, patient characteristics, associated injuries, hospital-resources, availability of assistants and surgeon preference and experience may all play a role in determining which positioning option is chosen. There are advantages and disadvantages to each, and little clinical evidence exists to aid in decision-making.

This research group completed a systematic review of the literature on patient positioning during antegrade nailing of femur fractures.¹² The review identified only three studies on this specific topic,^{13,14,15}. The best existing evidence of the previous literature comes from a prospective randomized trial led by Stephen et al (2002)¹⁵. The authors described that supine positioning without use of fracture table yielded better post-operative rotation than patients treated with a fracture table. However, this study did not compare the utility of lateral positioning, which is more commonly used in isolated femoral shaft fractures. Moreover, the study was unable to associate malrotation with patient important outcomes or gait abnormalities. This clearly leaves much uncertainty surrounding optimal patient positioning during the definitive treatment of these critical injuries.

For antegrade intramedullary nail, supine positioning is most commonly accompanied by a fracture (or traction) table. This surgical table secures the injured extremity and maintains it in a set position throughout the procedure using an adjustable amount of mechanical traction applied through a boot or skeletal traction pin, while using posts and straps to provide counter traction. While this may do an excellent job at obtaining length, it may be easy to mal-reduce comminuted fractures if keen attention is not paid to other anatomic reference points that help restore alignment and rotation¹⁵. This is vital, as the main reason for malpractice litigation following a femoral shaft fracture is failing to restore anatomic length, alignment and rotation¹⁶. While the traction table may be a useful tool, it can easily over-power the patient's own resting soft tissue tension, and lead to mal-reduction of the fracture. The most challenging intraoperative assessment is that of femoral rotation¹⁷. Numerous tools are used, including cortical width, cortical diameter, lesser trochanter profile and others¹⁸. The most reliable technique described in

recent papers is the lesser trochanter profile¹⁹, but it requires a true anteroposterior view of the pelvis, which can be challenging to obtain with the fracture table in situ.

In addition to this, numerous issues may arise secondary to prolonged procedures and application of traction. Flierl described a host of potential issues: perineal skin and soft tissue compromise from using a metal post between the patient's leg, neurologic impairment of the non-affected leg with either a femoral or peroneal nerve palsy, and iatrogenic compartment syndrome of the non-affected extremity²⁰. These can occur at a variable rate, but are serious and potentially avoidable complications. Lastly, not every hospital has easy access to a fracture table. They are expensive, routinely over \$200,000 including all orthopaedic extensions²¹, and are specialized tables designed exclusively for orthopaedic trauma. Fracture tables may not be a feasible or practical piece of equipment for some centres to invest in.

The use of the lateral position for intramedullary nail has been described for the past thirty years²², though rarely reported on in the literature. Patients who present with femur fractures are often multiply injured trauma patients, and as such surgeons and anaesthetists have been hesitant to place these patients in a lateral decubitus or even a modified lateral position, with a bump under the patient's hip, in the past. Their concerns stem from belief that a lateral position can worsen respiratory function and prolong extubation, leading to longer intensive care unit (ICU) stay, especially in patients who may have had thoracic injuries during their index traumatic event. However, results from the most recent cohort study suggest the opposite; that patients treated in the lateral position may have shorter ICU stay and reduced days on a ventilator, adjusting for patient risk in propensity based analyses²³.

Furthermore, part of the reluctance to use the lateral position may be due to lack of surgeon comfort. The commonly used technique of using the fracture table for femoral neck fractures and intertrochanteric hip fractures is easily applied for fixation of femoral shaft fractures. Converting the patient position to the lateral position yields a different radiologic perspective throughout the case though the surgical technique is identical.

To ascertain surgeon preferences, we conducted both a province wide survey through the Ontario Orthopaedic Association (OOA), Canadian Orthopaedic association (COA), and an international survey amongst members of the AO Trauma (AOT) group. The 197 respondents showed disparity and disagreement amongst standard of care for these significant injuries. Sixty-four (64) percent of surgeons surveyed in the AOT group said they prefer either sloppy lateral or direct lateral for antegrade fixation of femur fractures (AFFF). Interestingly, they reported that their colleagues, perhaps not members of the AOT, choose supine on a fracture table for antegrade fixation of femur fractures more than 65% of the time. Surgeons reported that lack of comfort and expertise (48.2%) were reasons for themselves not choosing a lateral position for AFFF. Furthermore, the respondents endorsed the significant complication risk of fracture table use, with 82% of respondents answering that they witness a traction table related injury at a rate greater than 1%. Lastly, 60% of respondents were interested in being part of this clinical trial, indicating the interest in and controversy surrounding this topic. Survey respondents reported that the main benefits of lateral positioning were ease of control of the fracture fragments throughout the entire procedure, as the leg is not under constant traction or draped outside of the sterile field. This finding has been reproduced when use of manual traction in a supine position

has been compared to fracture table in a prospective randomized trial, but never objectively assessed with a laterally positioned patient¹⁵. Lateral positioning allows the fracture fragments to be freely manipulated and muscles to find their resting tension, which may help better restore overall alignment. This trial also found that the use of the lateral position does not yield any traction related complications.

2.0 STUDY OBJECTIVES AND HYPOTHESIS

2.1 Feasibility Objectives

The primary objective of this pilot trial is to assess the feasibility of a definitive cluster randomized crossover trial to compare lateral positioning for antegrade fixation of femur fractures to standard supine positioning on a fracture table. The feasibility objectives are to determine our ability to: 1) enroll eligible patients across all participating clinical sites; 2) comply with the randomization treatment allocations; 3) obtain CT scans on participants within 6 weeks of their fracture; and 4) collect data on the case report forms (CRFs).

2.2 Objectives for the Definitive Trial (Clinical Objectives)

The secondary objectives of the pilot trial will be the clinical objectives of the definitive trial. The primary objective of the definitive trial is to determine if lateral positioning yields better rotational alignment of the operative limb. This will be determined through post-operative computer tomography (CT) scans. The secondary objectives of the definitive trial are to determine if lateral positioning affects: 1) health-related quality of life, 2) operative time, 3) use of intraoperative fluoroscopy, 4) conversion to open surgery, and 5) complications from use of the fracture table or from lateral positioning.

2.3 Study Hypothesis

We hypothesize that the pilot study will demonstrate feasibility for a larger definitive trial. For the definitive trial, we hypothesize that lateral positioning, when compared to supine positioning with a traction table, will lead to better rotational alignment as measured on postoperative CT scan. Furthermore, lateral positioning will have higher health-related quality of life, equal operative time, less intraoperative fluoroscopy time, fewer operative complications, and better gait velocity.

3.0 STUDY DESIGN

This will be a multi-centre pilot cluster randomized crossover trial of approximately 100 patients and two clinical sites. This pilot study will allow us to test a cluster crossover protocol and data collection methods before initiating a definitive trial. We require a pilot trial prior to a large multi-centre definitive trial to identify any issues with the methodology, study processes, and data collection, and to make any necessary changes to the protocol, study processes, and case report forms prior to large-scale implementation of a definitive trial.

This trial design will allow us to have direct evidence comparing the efficacy and safety of the two surgical interventions. The unit of randomization is the orthopaedic practices within

clinical sites (clusters) with individual patients being the unit of analysis. Recruitment for each treatment group will be performed in multiple iterations of approximately two-month periods. Each practice will initially be randomized to use either lateral or supine positioning with a fracture table. Upon completion of each two-month period, the practice will crossover to the alternative treatment allocation. This process of alternating treatment periods (crossovers) will continue until the minimum sample size is achieved (Figure 1). This approach has been used successfully in other orthopaedic trauma trials (PREP-IT).

4.0 METHODS

4.1 Study Setting, Cluster Eligibility, and Selection of Clusters

This study will be coordinated by the Methods Center at the Center for Evidence-Based Orthopaedics (CEO), McMaster University, Hamilton, Ontario. Clinical sites will be carefully screened prior to participation in the FLiP study. Cluster inclusion criteria are: 1) adequate research personnel infrastructure to manage the study; 2) commitment from all or most orthopaedic surgeons to participate in the trial; 3) ability to use the two interventions – lateral positioning with a radiolucent table and supine positioning with fracture table; and 4) adequate fracture patient volume. The exclusion criteria are: 1) lack of interest in the trial; 2) anticipated challenges with complying with the protocol; 3) conflicting studies, in the judgment of the Principal Investigators, that would inhibit patient participation; and 4) budgeting or contract constraints. Clinical sites that meet the eligibility criteria at this stage will be invited to participate in a series of teleconferences to review the study and clinical logistics in detail with members of the study team. During these calls, the study team will further vet the clinical sites to ensure that they meet the above cluster eligibility. Two clinical sites will be selected to participate in this pilot study. An additional two clinical sites will be selected as back-up sites, should some of the selected sites not initiate. Study personnel will document reasons for cluster ineligibility.

4.2 Participant Eligibility Criteria

Broad eligibility criteria will be used to increase the generalizability of the trial. The inclusion criteria are:

1. Adult aged 18 years of age or older
2. Mid shaft (Diaphyseal) femur fracture appropriate for antegrade fixation
3. Surgery performed by participating surgeon or delegate
4. Ability to obtain perioperative imaging (CT scans)
5. Provision of informed consent
6. Enrolled within 3 weeks of femoral shaft fixation

The exclusion criteria are:

1. Ipsilateral tibial fracture
2. Bilateral femur fracture
3. Ipsilateral femoral neck fracture
4. Ipsilateral acetabular fracture
5. Periprosthetic fracture

6. Pathologic fracture
7. Previous external fixation of femoral shaft fracture
8. Inability to be positioned in lateral decubitus because of a concomitant injury
9. Contraindications to CT imaging including impaired kidney/liver function, or lack of timely availability
10. Pregnancy (due to decubitus positioning)
11. Incarceration
12. Expected injury survival of less than 6 months
13. Terminal illness with expected survival of less than 6 months
14. Inability to provide informed consent (e.g. cognitive disability, language barrier, significant delirium or dementia)
15. Currently involved in study that does not permit co-enrolment
16. Likely problems, in the judgment of study personnel, with maintaining follow-up with the patient

4.3 Recruitment Strategy

4.3.1 Patient Screening and Consent

Patients aged 18 years of age and older who present to a participating clinical site for treatment of a femoral shaft fracture will be screened for participation within 3 weeks of their fracture. To screen patients for eligibility, designated study personnel at each clinical site will develop a patient enrollment plan. This plan will typically consist of daily participation in orthopaedic patient rounds and a review of daily listings of hospital admissions for patients with femoral shaft fractures. Upon identification, the study personnel will screen the patient for eligibility and if eligible, approach them for informed consent. Study participants must be enrolled within 3 weeks of their fracture(s) and enrollment may take place at any time within this window. If the patient is unable to provide informed consent (e.g., due to their injury) at the time they were initially identified, informed consent may be delayed until they are able to provide informed consent. Alternatively, if the patient is unable to provide informed consent, informed consent may be obtained from their proxy, with consent obtained from the patient when/if the patient is able to provide consent. Allowing informed consent from a patient's proxy healthcare decision maker will reduce the risk of recruitment bias against the most severely injured patients. The trial will be explained to patients with emphasis that there will be no negative implications should they choose not to be involved. A standardized consent form will be provided to patients which will be signed and stored securely by the research coordinator.

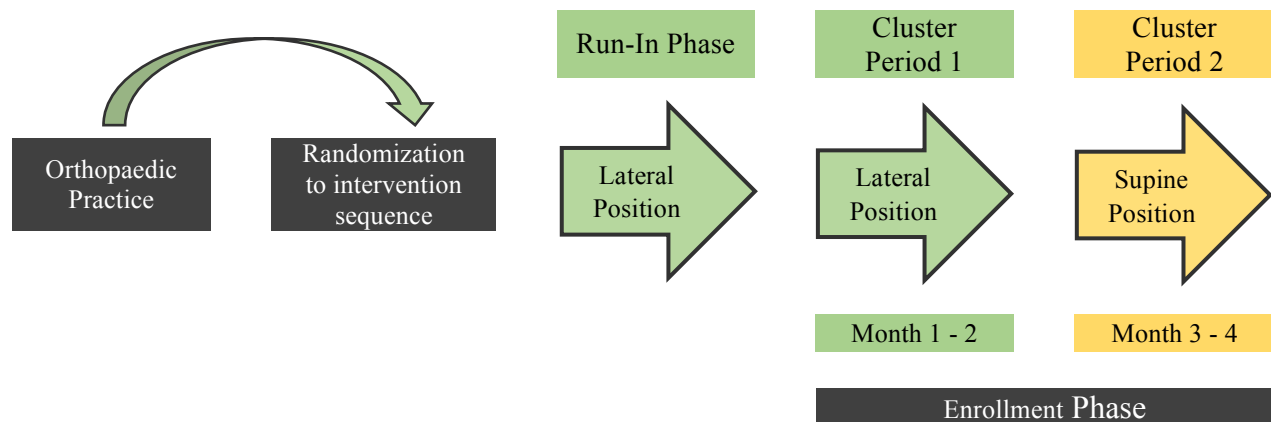
In addition, potentially eligible patients will be approached to participate in the trial, even if they did not receive the correct treatment intervention. This is consistent with the intention-to-treat principle (ITT) and is necessary to maintain the prognostic balance achieved during the cluster randomization. All screened patients will be classified as included, excluded, or missed. See Table 1 below for the Schedule of Events.

4.4 Randomization Methods

Treatment allocation will be determined using a cluster-randomized crossover trial design. The order of treatment allocation for each orthopaedic practice (cluster) will be randomly assigned using a computer-generated randomization table (1:1 allocation ratio). Each site will start with the initially allocated patient positioning for the first cluster period and crossover to the

other position for their second cluster period. This process of alternating treatments will repeat approximately every 2 months as dictated by the initial randomization. Randomization will be completed by personnel at the CEO Methods Center at the onset of the trial. Personnel from the Methods Center will notify personnel at each participating clinical site of their treatment allocation order.

Figure 1: Cluster Crossover Design



4.5 Blinding

The orthopaedic team (including the study coordinators) cannot be blinded to the treatment allocation as the two patient positions are visually distinguishable and these individuals need to lead the implementation of the cluster crossover protocol at their clinical site. The patients, outcome assessors (adjudicators), and data analysts will be blinded to the study treatment. Patients may become unblinded to their treatment through discussion with health care practitioners in follow up or through access to their operative reports; however, all study personnel will be instructed to not disclose positioning to patients. All interpretation of study results will initially be done in a blinded manner by developing two interpretations of the results. One interpretation will assume treatment A is lateral positioning, the other interpretation will assume it is supine with fracture table. Once the data interpretations for each assumption are finalized, the data will be unblinded and the correct interpretation will be accepted²⁴.

4.6 Description of the Interventions

4.6.1 Run-in Phase

Prior to initiating patient recruitment, each clinical site will begin using their randomly assigned patient positioning for eligible femoral shaft fractures (run-in period) to ensure that acceptable compliance is met before initiating participant enrolment. Acceptable compliance during the run-in phase will be defined as at least 5 eligible femoral shaft fracture patients with >90% of eligible patients receiving the allocated treatment arm or a minimum of one month in duration. The run-in phase may be extended up to 3 months, as deemed necessary by the CEO Methods Center. Study personnel at each clinical site will document compliance with administering the allocated treatment during the run-in phase and submit this weekly to the CEO Methods Center. Specifically, the weekly reports will include the total number of eligible femoral shaft fracture patients operated on, the proportion who received the assigned treatment intervention, and the proportion who did not receive the assigned intervention, along with details

about the deviations (e.g., name of attending surgeon, position used, rationale for not using the assigned positioning). This portion of the study protocol is for quality assurance during the initial implementation of the trial procedures. Femoral shaft fracture surgeries reviewed during the run-in phase will not be included in the trial. Similarly, these patients will not be approached for informed consent and no individual patient-level data will be submitted. CEO Methods Center personnel will review the weekly reports with each of the clinical sites and develop strategies, as needed, to ensure acceptable compliance during the run-in phase. This weekly communication will prevent any delays in transitioning to the participant enrolment phase.

4.6.2 First Intervention Phase

Once the initial run-in phase is completed, participant recruitment will begin with the clinical sites continuing to use the same patient positioning for all eligible femoral shaft fracture surgeries for a two-month period. Patients will receive the initially allocated treatment arm for all of their femoral shaft fracture management surgeries. Methods Center personnel will continue to monitor compliance with the assigned patient positioning over the enrolment phase and work collaboratively with the clinical sites to minimize cases in which a patient receives the incorrect positioning. These monitoring activities will coincide with site-specific procedures to maintain compliance for all patients. If a femoral shaft fracture requires multiple surgeries and the correct positioning is not used during each procedure, the patient will remain in the study and be analyzed using the allocated position (ITT principle).

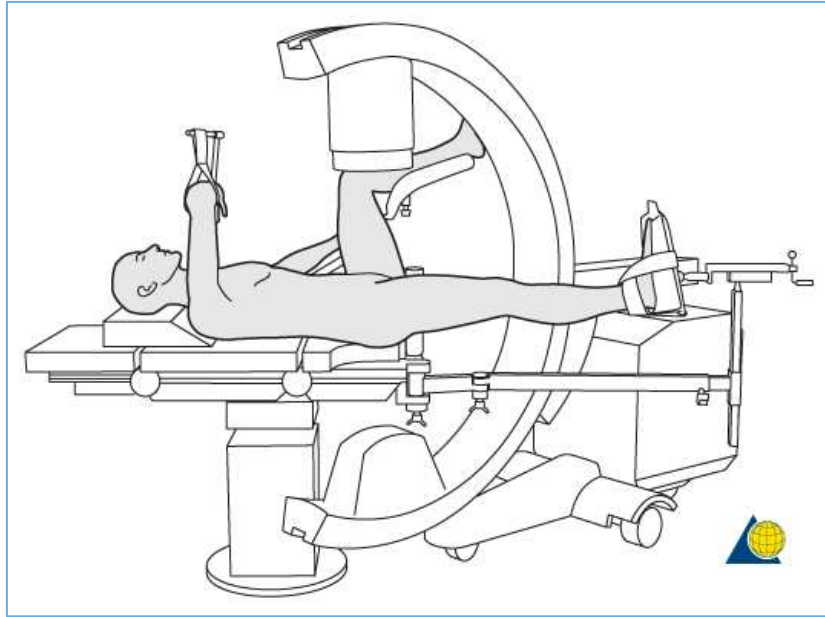
4.6.3. Second Intervention Phase

Once the first intervention phase is completed, each site will crossover to the opposite intervention. There will be no run-in phase for the second phase and each site will need to develop local procedures to ensure a successful crossover. Example procedures to minimize carry-forward of first intervention into the second intervention phase include: 1) changing study posters and notifications within the operating rooms; and 2) performing the crossover during the middle of the week to provide a few days' notice to the operating room staff. The enrolment goals and procedures will mirror the first intervention phase. Methods Center personnel will continue to monitor compliance with the assigned treatment intervention over the enrolment phase and work collaboratively with the clinical sites to reduce the risk of contamination.

4.6.4 Supine Positioning, Fracture Table

During the supine fracture table phase, patients will be positioned supine on a fracture table. The operative leg will be placed in a boot, attached to the traction limb. The non-operative leg will either be scissored away from the operating area in a traction boot (without traction placed), or placed in a stirrup at 90 degrees of hip flexion in hemilithotomy. A central post will be used to prevent patient movement during application of traction, and all bony prominences will be padded. Fluoroscopy will be obtained through standard practices. (**Figure 2**).

Figure 2: Supine Positioning, Fracture Table Schematic

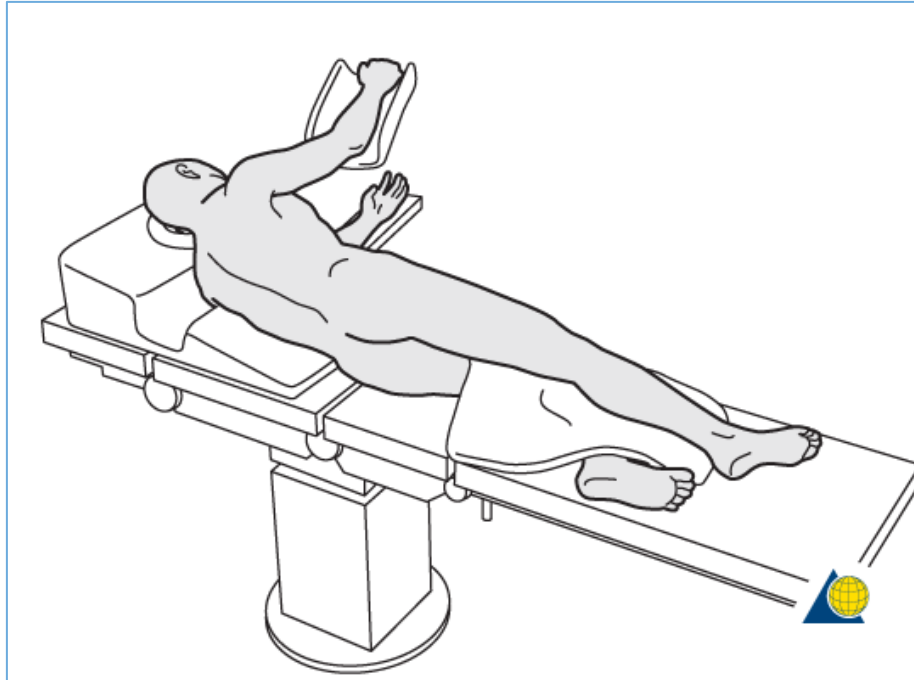


4.6.6 Lateral Positioning, Free drape

During the lateral positioning phase, patients will be placed in lateral position after anaesthetic has been provided. A beanbag will be placed below the patient, and the patient will be safely turned to a lateral position (**Figure 3**). The beanbag will be inflated, the leg will be prepped, and a free drape will be applied. No traction will be used. Alternatively, some participating sites may use stulberg positioners rather than an inflatable beanbag, based on hospital preference. This positioning mirrors the positioning utilized for the direct lateral, posterior or posterolateral approach to a total hip arthroplasty or hemiarthroplasty (**Figure 3**).

Use of a “sloppy” lateral positioning with placement of the operative limb in a minimum of 60° forward elevation through using a bump or sheet underneath the ipsilateral pelvis will also be considered acceptable. This will be documented on the case report forms.

Figure 3: Lateral Positioning Schematic



4.6.7 Multiple Procedures

If a femoral shaft fracture requires multiple surgeries, the same position should be used for all surgeries. If the correct positioning is not used during each procedure, the patient will remain in the trial and be analyzed using the allocated position (ITT principle).

5.0 OUTCOMES

5.1 Feasibility Outcomes

The feasibility outcomes are our ability to: 1) enroll eligible patients across all participating clinical sites; 2) comply with the randomization treatment allocations; 3) obtain CT scans on participants within 6 weeks of their fracture; and 4) collect baseline, surgical, and follow-up data on the case report forms. Feasibility outcomes will be collected on the case report forms, which include a screening log, randomization form, baseline form, surgical form, CT form, and follow-up form. From the case report forms, we can determine if the following success criteria are met:

- 1) 90% of eligible patients are enrolled;
- 2) 90% compliance with the randomization treatment allocations;
- 3) CT scans obtained within 6 weeks of their fracture in 95% of participants;
- 4) 95% completed data collection on randomization, baseline, and surgical case report forms, and 90% complete follow-up data on the case report forms.

5.2 Clinical Outcomes (Outcomes of the Definitive Trial)

The primary outcome will be *femoral malrotation of the operative limb*. Post-operative bilateral CT scans of the operated patients' lower extremity will be completed. Postoperative CT scans for femoral shaft fractures represents the standard of care across academic centres²⁵. A blinded radiologist who serves on the Adjudication Committee will review each CT scan and assess length discrepancy, internal or external rotation of the femur compared to the longitudinal

axis, and mal-alignment or mal-reduction of fracture components. Preferred measurement of malrotation will be completed by a protocol described by Tornetta *et al*²⁶. Malrotation will be measured with the CT scan using three 3-mm cuts through the femoral neck region and three more through the condylar region of both femora simultaneously. Anteversion / rotation will be defined as the angle between the axis of the femoral neck and the line drawn tangent to the posterior femoral condyles. The degree of rotation will be defined as the difference between the anteversion on the operative leg and the anteversion on the non-operative side. Rotation will be analyzed both as a categorical and continuous value. The best available literature defines clinically significant malrotation as more than 15 degrees difference from the contralateral limb in either internal or external rotation^{27,28}. Malrotation greater than this amount is associated with gait abnormalities including abnormal hip rotation, pain and foot progression angles – all causing functionally significant limitations for patients. Therefore, more than 15 degree difference in either internal or external rotation will be evaluated as malrotated. Additionally, we will assess rotation as a continuous variable as well, with 0 degrees representing no difference in rotation from the contralateral femur.

Health-related quality of life will be assessed with the EQ-5D. The EQ-5D is a standard questionnaire that will be completed by participants at the time of consent and will ask about their pre-injury status and at the six month follow up visit asking about their current status. The EQ-5D score represents patient reported health-related quality of life in five domains – mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. The EQ-5D²⁹ will be administered by study personnel at the 6 week, 3 month, and 6 months visits or it may be administered over the telephone, standard mail, or sent to the participant to complete via email using the REDCap Cloud electronic data capture (EDC) system.

Operative time per case will be defined as the time the patient is brought into the operating room and ending once the patient has procedural wounds closed. This is documented as part of the operative notes. *Fluoroscopy time* is defined as the total time that fluoroscopy is used and is recorded on the C-Arm used for intraoperative imaging.

Conversion to open surgery is defined as any secondary incision at fracture site >5 cm. This incision facilitates open reduction and is viewed as a surrogate measure of difficulty achieving the appropriate reduction with closed manipulation. Conversion to open surgery is documented in the operative note.

Standard operative table and fracture table complications include all potential neurological injuries (pudendal, peroneal and femoral nerve palsies), skin injuries including skin blisters, ulceration, and skin tears from use of traction boot apparatus. These will also be documented in the operative note as standard of care.

Serious adverse events will also be recorded on the case report forms and promptly submitted to the Methods Centre. Serious adverse events will be submitted to the local or central Research Ethics Board (REB) as per the required reporting processes. They will be reviewed by the Medical Monitor (See Section 8.6.5).

5.8 Data Collection and Participant Follow Up

Table 1 presents a summary of study procedures and data collection time points. After obtaining informed consent, study personnel will record the screening, randomization, baseline, and surgical data on the case report forms. They will obtain this information directly from the participant or proxy, from the participant's medical chart, and the participant's treating orthopaedic surgeon or other health care providers. Data collection points include patient characteristics and injury details such as age, gender, comorbidities, mechanism of injury, AO fracture classification, open fracture status based on Gustillo Anderson, classification, socioeconomic status, and other injuries. Surgical data and in-hospital data will include operative time, fluoroscopy time, the surgical management of the fracture(s), the position used, complications, and conversion to open surgery. Peri-operative data will include the length of hospital stay. Study participants will be followed at 6 weeks, 3 months, and 6 months post-fracture. At each visit the participant will be asked to complete the EQ-5D and asked if they have experienced any SAEs. Their medical record will also be reviewed to verify the information provided.

In cases where the participant does not return to the clinic, study personnel will contact the participant by telephone, text, email or standard mail. Several strategies may be used to maximize follow-up including: 1) at the time of enrolment, each participant will provide their own telephone number, as well as the name and address of a primary care physician, and the names and phone numbers of three other people at different addresses with whom the participant does not live with and who is likely to be aware of the participant's whereabouts; 2) participants will receive a reminder card upon discharge for their next follow up visit by the clinical site study personnel; 3) participants will receive text message reminders; 4) follow-up will coincide with normal surgical fracture clinic visits; and 5) if a participant refuses or is unable to return for the follow-up assessment, study personnel will determine his/her status with regard to major study outcomes by telephone, text, or email contact with the participant or the provided alternate contacts. Given these are standard of care visits and the participants will be receiving ongoing orthopaedic care for their acute fractures, minimal loss to follow-up is expected. Participants will not be deemed lost to follow-up until the 6-month visit is overdue and all attempts to contact the participant have been exhausted. Participants will not be withdrawn from the study if the study protocol was not adhered to (e.g., allocated treatment not received, missed follow-up visits, etc.). The reasons for participants being withdrawn from the study will be documented (e.g., withdrawal of consent or lost to follow up). We have used this approach in our other multi-center trials (e.g., SPRINT³⁰, TRUST³¹, FLOW³², FAITH³³, HEALTH³⁴, etc.).

Table 1: Schedule of events

Event	Baseline Visit (0-21 Days)	6 Week Visit (21- 56 days)	3 Month Visit (57-137 days)	6 month Visit (138-228 days)
Screening	X			
Consent	X			
Demographics characteristics	X			
Fracture and injury details	X			
Treatment allocation	X			
Surgical details				
Positioning				

Operative time	X			
Fluoroscopy time	X			
Fracture table complications	X			
Conversion to open procedure	X			
Surgical management details				
Peri-operative details				
CT scan	X*			
Serious adverse events	X	X	X	X
EQ-5D	X	X	X	X

*CT scan to be completed within 6-weeks (42 days) of the fracture

6.0 STATISTICAL METHODS

6.1 Sample Size for Pilot Study

Since the feasibility objectives in our pilot study do not lend themselves to traditional quantitative sample size calculations, we selected a sample size of 2 clusters and approximately 100 participants to assess the feasibility of a definitive large trial. Implementing the protocol at 4 clusters will allow us to adequately address our feasibility objectives and determine if we should proceed with a definitive trial. The PREP-IT team conducted a VanGuard Phase at two clusters and successfully confirmed feasibility and refined the case report forms³⁵. Additionally, other orthopaedic fracture trials that follow a traditional randomized controlled trial design conduct pilot studies with sample sizes ranging from 60 to 100 participants³⁶.

6.2 Sample Size for the Definitive Study

The sample size for our definitive trial will be based on the primary outcome of evaluating risk for femoral malrotation following intramedullary nailing of femoral shaft fractures. Assuming an ITT principle for the analysis, the sample size was calculated based on a cluster crossover design with the cluster as the unit of randomization and the patient as the unit of analysis. For complex study designs, such as a cluster-randomized crossover trial, simple formulas to calculate sample size or power may not capture the expected variability from the observed data. Currently, there are no established methods for performing a simple sample size calculation for a cluster-randomized crossover trial. As a result, simulation methods have been employed as described by Reich *et al.*, to obtain empirical power calculations based on a feasible number of recruiting clusters and the expected number of open fracture patients³⁷.

The simulation estimates are designed to detect a difference between the treatment groups, accounting for between hospital variability inherent to a cluster-crossover trial design. Malrotation greater than 15° has been documented to occur at a rate between 10-26% following antegrade intramedullary nailing of femoral shaft fractures^{38,39}. We have assumed that lateral positioning will yield a risk ratio of 0.5 for femoral malrotation¹⁵. With a baseline incidence of approximately 20%, this leads to a 10% absolute risk reduction in femoral malrotation.

Unpublished simulation data suggest that increasing the number of period crossovers can increase the statistical power of a given sample size. To ensure the most conservative sample size estimate, we have based our sample size assumptions using a single crossover, 2 period design. Assuming 10 recruiting clusters, a 10% loss to follow-up rate and applying the between-cluster variance of 0.095 observed in previous cluster crossover trials³², a minimum of xx femoral shaft patients will be enrolled. This will achieve greater than 80% power.

6.3 Analyses of Pilot Study Data

We will follow the CONSORT extension to pilot trials in reporting the results of this pilot trial.¹¹ Briefly, the baseline characteristics, fracture and injury characteristics, surgical details, peri-operative care data, and feasibility outcomes will be summarized using descriptive statistics reported as means (standard deviation (SD)) or medians (first quartile, third quartile) for continuous variables depending on their distribution and counts (percentage) for categorical variables. We will use a statistical package (e.g. R, SPSS, SAS) to perform all analyses. A detailed Statistical Analysis Plan will be developed prior to the close-out of the pilot study.

6.3 Overview of the Analyses of Clinical Outcomes

If the feasibility analysis demonstrates a successful pilot study and the study team makes the decision to proceed with a definitive trial and include the participants enrolled in the definitive trial, we will not analyze the clinical outcomes data for the pilot study. Conversely, if the pilot study participants are not going to be included in the definitive trial, we will analyze the clinical outcomes as per below. We will consider the clinical analyses of the pilot study data as exploratory. Therefore, we will not adjust for multiple testing and not draw definitive conclusions. Additionally, we will not conduct the subgroup analyses described below in the analysis of the pilot study data, as per the CONSORT recommendations.

The analysis and reporting of the results will follow the CONSORT guidelines for reporting of cluster-randomization trials. The process of patient enrollment and flow throughout the study will be summarized using a flow-diagram. Patient demographics, fracture, injury, and surgical variables will be summarized using descriptive summary measures expressed as mean (standard deviation) or median (interquartile range) for continuous variables depending on the distribution, and number (percent) for categorical variables. An ITT principle will be adopted to analyze all outcomes and the unit of analysis will be the individual patients. Missing data will be assumed to be missing at random and will be handled with multiple imputation.

The primary analysis will compare the treatment groups on the rotational alignment of the operative limb outcome and the secondary analyses will compare the secondary outcomes as listed in Section 5.0. The secondary comparison will be conducted in accordance with best practice guidelines for secondary analyses. For all models, the results will be expressed as effect (odds ratios for binary outcomes; mean difference for continuous outcomes), corresponding two-sided 95% confidence intervals, and associated p-values. All statistical tests will be performed using two-sided tests at the 0.05 level of significance. P-values will be reported to three decimal places with values less than 0.001 reported as <0.001. All analyses will be performed using a statistical package (e.g. R, SPSS, SAS).

Adopting an ITT principle, multilevel regression models will be used. Correlation structures will be fit based on the observed between cluster and between period effects. A robust sandwich estimator will be used to analyze the primary and secondary outcomes.

For the primary outcome, rotational alignment of the operative limb outcome will be the dependent variable and the type of positioning (treatment group) will be the independent variable. For the secondary outcomes, each secondary outcome (as listed in Section 5.2) will be

the dependent variable and the type of positioning (treatment group) will be the independent variable. For all analyses, multiple imputation will be used to handle missing data.

As the optimal methods for analyzing cluster crossover trials continue to evolve, the final statistical modeling technique to be used will be determined in accordance with contemporary best practices prior to the completion of participant follow-up. A separate Statistical Analysis Plan will be developed prior to study closeout. **Table 2** below shows a summary of the study outcomes, corresponding hypotheses, and currently proposed methods of analysis.

Table 2 – List of outcomes with associated hypotheses and measurements

Variable/Outcome	Hypothesis	Outcome Measure	Method of Analysis
Femoral Malrotation	Lateral positioning will have a lower risk of malrotation	CT scan measuring femoral malrotation	Multi-level regression model
Health-Related Quality of Life	Lateral positioning will result in better health-related quality of life	EQ-5D	Multi-level regression model
Operative Time	Lateral positioning decreases operative time	Time from anaesthesia ready to skin closure completed	Multi-level regression model
Fluoroscopy Time	Lateral positioning decreases fluoroscopy time	Intraoperative time of fluoroscopy used	Multi-level regression model
Conversion to Open surgery	Lateral positioning decreases need to open at fracture site	Use of >5 cm incision at fracture site to manually reduce fracture (i.e. open reduction). Categorically measured as yes/no	Multi-level regression model
Operative table complications (skin breakdown, nerve injury)	Lateral positioning will have a lower complication rate	Number of complications	Multi-level regression model

6.4 Subgroup Analyses

We will not conduct any subgroup analyses in the pilot trial. If relevant, we may consider subgroup analyses for the definitive trial. Potential subgroups include obese patients, those with chest trauma (including rib fractures, lung contusions, flail chest, etc.) and older patients (defined as age >65).

6.5 Interim Analysis

We will not conduct an interim analysis as this is a pilot trial. We will not stop the trial for benefit, and we will consider advice from the Medical Monitor regarding stopping for harm.

7.0 DATA MANAGEMENT

7.1 Case Report Forms and Data Transmission

Clinical sites will be provided with the trial case report forms prior to initiation of enrollment. Research personnel at each clinical site will submit the required data, as detailed on the case report forms, to the Methods Center using the REDCap Cloud electronic data capture system. Clinical site personnel will receive a unique login and password for the REDCap Cloud system and will be able to view and modify data for participants recruited at their clinical site.

7.2 Data Integrity

The REDCap Cloud system uses a variety of mechanisms for checking data at the time of entry including skip logic, range checks, and data type checks. Upon receipt of new data, the personnel at the Methods Center will query all missing, implausible, or inconsistent data. Clinical site personnel will be able to review of open queries in the system and will be required to respond promptly.

8.0 ETHICS AND DISSEMINATION

8.1 Ethical Regulations

This study will be conducted according to international standards of international council for harmonization – good clinical practice (ICH-GCP) applicable government regulations, and institutional research policies and procedures. The trial has been registered at ClinicalTrials.gov.

8.2. Research Ethics Approval

The Methods Centre at McMaster University will receive ethics approval from Clinical Trials Ontario (CTO) REB prior to the initiation of the trial activities. Each participating site will also receive ethics approval prior to trial initiation either through a central REB or a local REB. Prior to local commencement of the study, each clinical site will provide the Methods Centre with a copy of their ethics approval.

8.3 Consent Process

In many cluster randomized comparative effectiveness trials, a waiver of consent is obtained from the REB of Record. The rationale for the waiver of consent is that all patients will receive treatments that are effective and within standards of care, they will receive one of the study treatments as part of their routine care regardless of study participation, the data collection is minimal and obtained from the patient's medical records, the trial involves no more than minimal risk to the patient, and that the waiver of consent will not adversely affect the rights and welfare of the patient. These concepts apply to the FLiP Trial as it is comparative effectiveness research where patients will be placed into one intraoperative position regardless of their participation in the study.

Additionally, patients are not included in the decision-making process for the choice of intraoperative positioning, and, in most situations, they are not even aware of which positioning

is used. However, in contrast to many cluster randomized crossover trials, FLiP study personnel will need to contact participants directly to collect baseline and outcome data, as this information cannot be reliably obtained from the patients' medical records. Therefore, study personnel will obtain informed consent from patients prior to data collection. This consent process will allow study participants to be informed about the study rationale and provide consent for ongoing surveillance and data collection.

To increase enrollment and to avoid missing potential study participants, the consent process may take place up to 3 weeks post-injury, before discharge from hospital. This approach has been used in other orthopaedic trauma trials, as obtaining consent prior to the patient's first surgery could add undue decision making stress to a patient who is awaiting surgical management of a serious extremity injury; allowing consent after their surgery would likely facilitate an improved consent process³⁵.

The consent process will typically take place in the patient's hospital room or at their first fracture clinic appointment. If the patient is unable to provide informed consent (e.g., due to their injury, language restrictions) within 3 weeks of their fracture, informed consent will be obtained from their proxy. To obtain informed consent, delegated study personnel should follow the below procedures:

- Present study information in a manner that is understandable to the potential participant/proxy.
- Discuss the study with the potential participant/proxy and answer any questions he or she asks.
- Allow the potential participant/proxy an opportunity to discuss participation with their family, friends, or family physician, if desired.
- Confirm that the participant/proxy understands the risks and benefits of participating in the study and that their participation is voluntary.
- Complete and obtain signatures for informed consent form and obtain contact information from the participant/proxy.
- Provide/send the participant/proxy with a paper/electronic copy of the signed consent form.

Consent may be obtained electronically or using pen and paper consent forms, as approved by the REB of Record. The process of obtaining and documenting informed consent will be completed in accordance with local Good Clinical Practice recommendations. Consent procedures and forms, and the communication, transmission and storage of patient data will comply with the REB of Record.

Upon providing informed consent, study participants will be followed for 6 months from their fracture. Given the short follow-up time, the need for a regular reassessment of consent will not apply; however, participants may withdraw their consent at any time.

8.4 Confidentiality

Information about study participants will be kept confidential and managed in accordance with the following rules:

- All study-related information will be stored securely

- All study participant information will be stored in locked file cabinets within locked offices accessible only to study personnel
- All paper and electronic CRFs will be identified only by an anonymized participant ID code
- All study databases will be password-protected

Communication, transmission and storage of patient data will comply with the applicable ethics committee. If a participant revokes authorization to collect or use personal health information, the participating clinical site retains the ability to use all information collected prior to the revocation of participant authorization. For participants who have revoked authorization to collect or use personal health information, attempts should be made to obtain permission to collect at least vital status (i.e., primary and secondary outcome data) at the end of their scheduled study period.

8.5 Protocol Amendments

Any amendments to the study protocol that may affect the conduct of the study or the potential safety of, or benefits to, participants (e.g., changes to the study objectives, study design, sample size, or study procedures) will require a formal amendment to the protocol. Any protocol amendments will be approved by the Principal Investigators, the CTO REB, local REBs, and funders (as needed). Participating clinical sites will also be required to submit amendment requests to their local ethics committees to obtain approval for the amendment, and to provide the Methods Centre with a copy of this approval. Administrative changes (e.g., minor corrections or clarifications that have no effect on the way the study is conducted) will not need to undergo a formal amendment process.

8.6 Safety and Adverse Events

8.6.1 Adverse Event Definition

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study.

8.6.2 Serious Adverse Event Definition

Adverse events are classified as serious or non-serious. A serious adverse event (SAE) is any AE that meets at least one of the following criteria:

- Fatal
- Life-threatening
- Requires or prolongs hospital stay
- Results in persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- An important medical event

8.6.3 Unanticipated Problems Resulting in Risk to Participants or Others

Any incident, experience or outcome that meets all the following criteria should be considered an unanticipated problem that results in risk to participants or others:

- Unexpected in nature, severity, or frequency (e.g., not described in study-related documents such as the ethics-approved protocol or Informed Consent Form, etc.);

- Related or possibly related to participation in research (i.e., possibly related means there is reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at greater risk of harm (including physical, psychological, economic or social harm).

Unanticipated problems resulting in risk to participants or others encompass more than what one usually thinks of as adverse events. ‘Problems involving risk’ may not necessarily result in harm. For example, misplacing a participant’s study records containing identifiable private information introduces the risk of breach of confidentiality. Confidentiality may or may not be breached, but either way this would be a reportable event. Risks to other must also be reported. For example, an unexpected outburst during questionnaire administration by a study participant that put study personnel at risk would be a reportable event.

8.6.4 Clinical Site Reporting

All SAEs or unanticipated problems resulting in risk to participants or others are to be reported to the Methods Centre immediately. Participating clinical sites are responsible for reporting SAEs to the Methods Centre via the REDCap Cloud EDC system. Significant new information on ongoing SAEs should also be promptly provided to the Methods Centre via the REDCap Cloud EDC system. Unanticipated problems resulting in risk to participants or others are also to be promptly reported to the Methods Centre via telephone or email.

Participating clinical sites are responsible for reporting SAEs and unanticipated problems resulting in risk to participants or others to their local ethics committee, or a central ethics committee, in accordance with local reporting requirements. Copies of each report and documentation of ethic committee notification and receipt will be kept in the participating clinical site’s study file.

8.6.5 Safety Monitoring

As per the FDA guidance document the *Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors*, a Medical Monitor (orthopaedic surgeon) will oversee the safety of the trial participants and the overall conduct of the trial. The Medical Monitor will be responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study. The Medical Monitor will frequently review enrollment and demographic summaries, listings of protocol deviations, and summaries and listings of SAEs. He/she will advise the Principal Investigators and study team on any concerns related to participant safety and trial conduct, and will make recommendations for the study to continue as designed, for study termination, for study continuation with major or minor modifications, or temporary suspension of enrollment until some uncertainty is resolved.

8.7 Dissemination Policy

Results from the study will be submitted for publication regardless of whether or not there are significant findings. Every attempt will be made to ensure that the amount of time between completion of data collection and release of study findings is minimized. The Methods

Centre will also be responsible for reporting required results on clinicaltrials.gov or other applicable clinical trials registry.

9.0 SUBSTUDIES

9.1 Gait Analysis Sub-Study

9.1.1 Background

We will conduct a sub-study to investigate differences in gait between the two treatment groups. We will invite 30 consecutive participants from each treatment group to participate in this sub-study at 6 months post-fracture. Only patients who have been treated at Hamilton Health Sciences – General Site will be included in the gait analysis sub-study. The only additional eligibility criteria is to provide consent for the sub-study. Consent will be acquired at 6 months follow up, separate from the initial consent from the larger study. The gait analysis will be performed using a clinical instrumented gait analysis system (Optitrack) in the orthopaedic clinic at the Hamilton Health Sciences - Juravinski Site. The system is a passive optoelectronic camera system that will be used to track the three-dimensional position and orientation of the lower extremity limb segments of the patients during over ground walking gait. Using previously developed and published gait kinematics protocols and analyses^{40,41}, we will capture and model magnitudes and patterns of three-dimensional angles of the hip, knee and ankle joints, as well as summary gait metrics including walking velocity, stride length, and stance/swing percentages. A matched cohort of patients, from an existing database of healthy individuals, will be used to compare study patients to “healthy cohorts” to show the extent of gait dysfunction.

9.1.2 Sample Size Calculation

A recent systematic review showed that most minimal clinically important differences (MCIDs) of walking speed fall between 0.10 and 0.17 (mean 0.14). We calculated a range of sample size estimates for varying values of walking speed differences and standard deviations that are likely based on the systematic review. These estimates are shown in the table below ($\alpha = 0.05$, power = 80%, loss to follow-up = 10%). With 60 participants (30 per group) in this biomechanical study, we will have sufficient power to detect the differences for the situations shown in green in the table below. Therefore, we have selected 60 as our sample size for this study.

Table 3: Sample Size Estimate for the Gait Analysis

Difference in Walking Speed Between Groups									
Standard Deviation		0.10	0.11	0.12	0.13	0.14	0.15	0.16	0.17
	0.11	60	50	44	36	32	28	26	22
	0.13	84	70	58	50	44	38	34	30
	0.15	110	92	78	66	58	50	44	40
	0.17	140	118	98	84	74	64	56	50

$\alpha = 0.05$, power = 80%, loss to follow-up = 10%

9.1.2 Statistical Analyses

Principal component analysis (PCA), a multivariate statistical pattern recognition and data reduction technique, has been used in previous gait studies to identify discriminatory features of gait (REF). Principal components (PCs) were for hip flexion, adduction and rotation

angles, knee flexion, rotation and adduction, as well as 3D hip and knee moments. Regression models will be used to examine differences in patient positioning while adjusting for age, sex, and interaction effects for each set of PC scores for the angle and moment waveform data. A full protocol on PCA can be found in Journal of Gait Posture⁴².

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